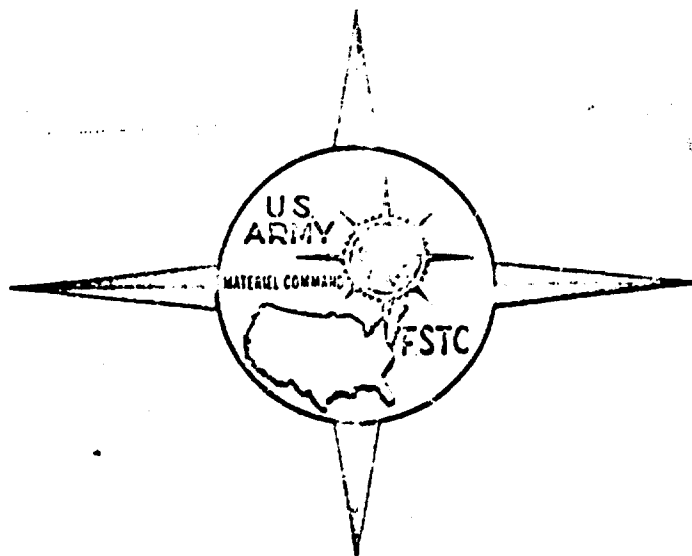


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TRANSLATION

A STUDY OF THE DYNAMICS OF THE BACTERIOLOGICAL PROCESS DURING
TREATMENT OF EXPERIMENTAL TULAREMIA WITH KANAMYCIN,
CHLORTETRACYCLINE AND STREPTOMYCIN

COUNTRY: USSR

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by Ye. M. Tsvetkova

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Abstract: Guinea pigs infected with lethal doses of tularemia bacteria displayed a marked decrease in number of bacteria in organs and tissues after administration of Kanamycin, chlortetracycline or streptomycin was begun at the height of the fever, about the fourth day. After the 10-day treatment was discontinued most animals were found free of bacteria; however, some suffered recurrence with some increase in number of bacteria in the organs. Kanamycin and streptomycin yielded best results. Chlortetracycline treatment was more difficult and less effective because of the insufficient dosage and treatment time used because of its toxicity for guinea pigs.

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A STUDY OF THE DYNAMICS OF THE BACTERIOLOGICAL PROCESS
DURING TREATMENT OF EXPERIMENTAL TULAREMIA WITH KANAMYCIN,
CHLORTETRACYCLINE AND STREPTOMYCIN

- USSR -

[Following is a translation of an article by
Ye. M. Tsvetkova, Laboratory of Tularemia
(Head: Professor N. G. Olsuf'yev, Corresponding Member of the Academy of Medical Sciences USSR) of the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, Academy of Medical Sciences USSR, Moscow, in the Russian-language periodical Antibiotiki (Antibiotics), No 3, 1966, pages 253-257.]

There are several reports on the highly effective therapeutic action of some antibiotics for tularemia; streptomycin, Kanamycin, and chlortetracycline deserve special attention.

There is one paper on the study of the dynamics of the bacteriological process during experimental tularemia treated with antibiotics, which submits the results of experiments performed on albino mice, using streptomycin, chlortetracycline, and levomycetin [1].

We performed experimental work for investigation of the dynamics of the bacteriological process during treatment of tularemia in guinea pigs with Kanamycin, chlortetracycline, and streptomycin of Soviet manufacture.

The animals were infected by subcutaneous injection of virulent tularemia strain No 503, maintained in the laboratory by passages through guinea pigs. The infection dosage constituted 100 Dclm. Two to four guinea pigs were destroyed at certain intervals and their regional lymph nodes, spleen and blood were examined. In the case of treatment with Kanomycin and chlortetracycline, the number of bacteria in the tissues was determined by bacteriological and biological methods; in the case of streptomycin treatment, bacteriological methods were used.

The organ to be examined was first weighed and the volume of blood removed was measured; after which the material was meticulously triturated in a mortar with saline, in a proportion of 1:10; from the obtained suspension dilutions were then made: 100, 1000, 10,000-fold, etc. Portions of 0.1 ml [milliliter] of the diluted material were inoculated on blood fish-yeast agar with glucose and cystine (three test tubes for each dilution) and concurrently, 0.1 ml of the last two or three dilutions were administered subcutaneously to the albino mice (two mice for each dilution). Upon calculation of colonies we obtained data which coincided with the data from biological examination referable to the number of bacteria per gram of examined tissue.

Eighteen untreated guinea pigs infected along with all of the animals served as a control. Two control guinea pigs were destroyed at each interval (4, 6, 7, and 8 days) after infection and a regional lymph node, spleen and blood were examined. In the guinea pigs that were destroyed four hours after infection, tularemia bacteria were found in the regional lymph node and in the spleen in a quantity of 100,000 to 10,000,000 bacterial cells/gram of tissue, and isolated bacterial cells were found per milliliter of whole blood. After six days, there was a ten to 100-fold increase in number of tularemia bacteria in the regional lymph node, spleen, and blood, and after seven to eight days it already constituted from 10 million to 10 billion bacterial cells in the regional lymph node, from 10 million to 1 billion in the spleen/gram of tissue, and up to 1000 to 10,000 bacterial cells/ml of blood. These data are consistent with those that have been published [2].

Kanamycin was injected subcutaneously into the guinea pigs: daily dosage -- 20,000 units, two injections daily; the course of treatment lasted ten days when it was begun at the height of the fever (fourth post-infection day). Even two days after the start of treatment we observed some (ten to 100-fold) decrease in number of tularemia bacteria in the regional lymph node and spleen as compared to the untreated animals. Six to eight days after start of treatment, the guinea pigs no longer presented fever, while their organs were almost free of tularemia bacteria. Six to seven days after treatment stopped some of the guinea pigs suffered a recurrence of the disease associated with fever and some increase in number of bacteria in the organs examined, which however did not exceed 1000/gram of examined tissue. Two of the guinea pigs which did not have a recurrence were destroyed 40 days after termination of treatment (on the 55th day of the experiment); no tularemia bacteria were found in their organs.

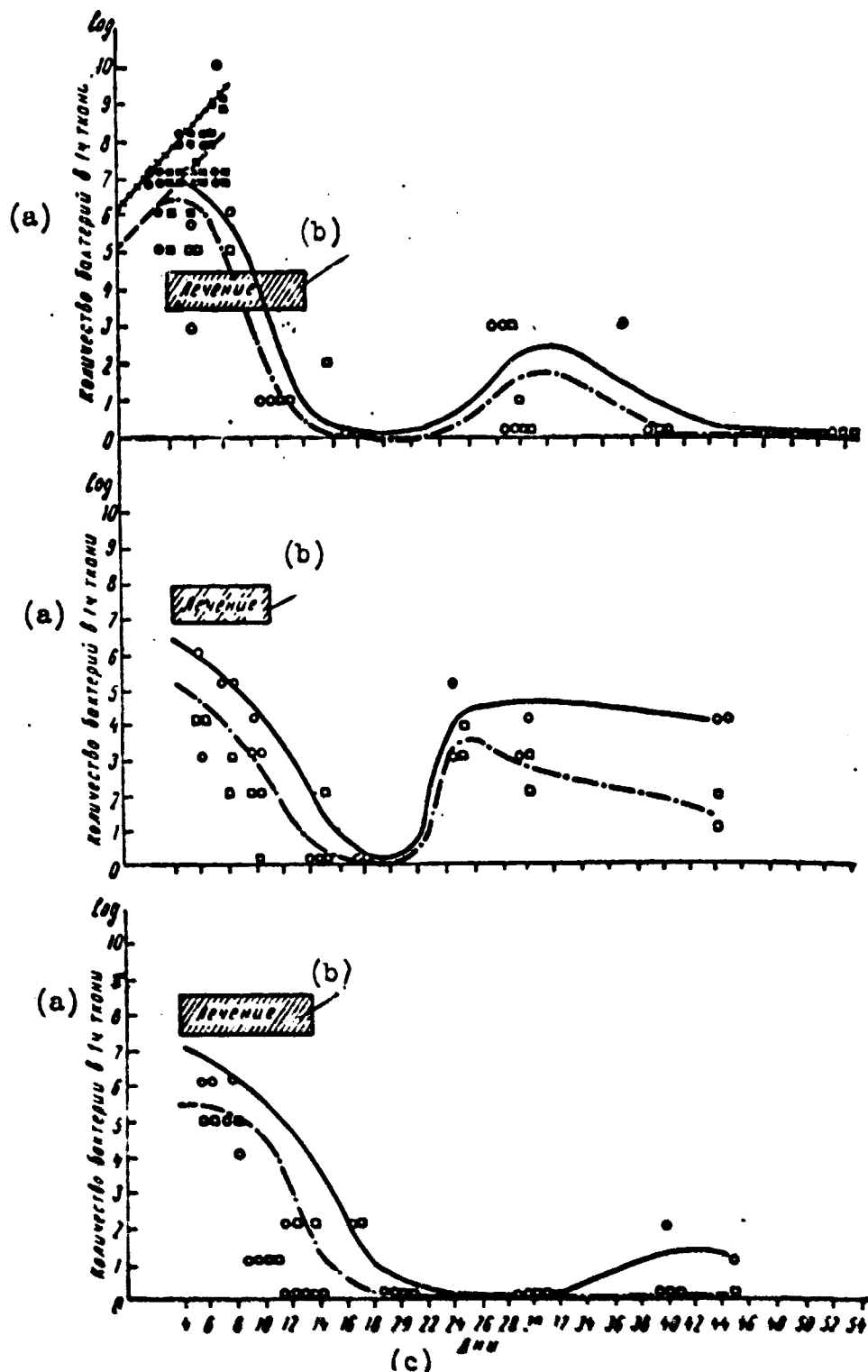
Chlortetracycline is toxic for guinea pigs and this added difficulty to our experiments. We used a small single

dose of chlortetracycline (a total of 10 milligrams [mg]) and administered it once subcutaneously at a 48 hour interval. Treatment was instituted four days after infection when the guinea pigs presented fever and after having received only four injections. There was a significant decrease in number of bacteria in the spleen and regional lymph node two days after treatment and especially four to six days after start of treatment. No bacteria were found in the blood at all examinations. Six hours after the start of treatment, the number of bacteria in the spleen was 1000 -- 100,000 times smaller in the treated animals, and in the regional lymph node it was 1000 -- 10,000 times smaller than in the control, untreated animals.

Five to eight days after treatment was discontinued we found no tularemia bacteria in the examined organs of most treated guinea pigs. However during this period, in the surviving guinea pigs there was a fever, which indicated a recurrence of the disease. These guinea pigs were destroyed 25 -- 45 days later and tularemia bacteria were found in the regional lymph node and spleen; in some instances numbering a considerable figure (up to 100,000/gram of regional lymph node tissue and up to 10,000/gram of spleen).

We attribute the inadequate effect of chlortetracycline treatment to the low dosage and limited period of administration, but we could not increase the dosage and increase the time since this would have caused the animals' death due to their high sensitivity to chlortetracycline. Perhaps too there was also a very rapid suppression of bacteria under the influence of chlortetracycline which was reflected in the development of immunity as noted in experiments on albino mice [1].

Subcutaneous treatment with streptomycin (daily dose: 30,000 units, two injections daily, treatment course; 10 days) resulted in a 100 -- 1000-fold decrease in tularemia bacteria in the regional lymph node and spleen as early as the second to fourth day, as compared to the control animals. After six, eight, and ten days of treatment the guinea pigs no longer ran a fever, and in most instances we found no tularemia bacteria in their organs; only in a few animals were isolated bacteria present in the regional lymph node. Four to eight days after termination of the treatment, four out of the six guinea pigs had a recurrence of the disease associated with a fever. The second fever wave lasted for three to eleven days. In three of the guinea pigs which had a recurrence and which were destroyed 20 -- 35 days after treatment was discontinued, tularemia bacteria were found only in the lymph nodes and even there in a very limited quantity (10 -- 100/gram of tissue). One of the guinea pigs in this group died at the height of a recurrence, and 100,000 tularemia bacteria were found in



Changes in quantity of *Francisella tularensis* per gram of tissue from a regional lymph node and spleen in guinea pigs infected subcutaneously with 100 Dclm -- untreated (control group) and treated animals. Top curve -- Kanamycin treatment; Second from the top -- Chlorotetracycline treatment; Third from the top -- streptomycin treatment; 1 -- lymph node; 2 -- spleen of untreated (control) animal; 3 -- lymph node; 4 -- spleen of treated animal; symbols -- factual data, extrapolation lines: along the ordinate -- quantity of bacteria per gram of tissue, along the abscissa -- time of infection (in days); a -- quantity of bacteria/one part of tissue; b -- treatment c -- days

its regional lymph node, and 10,000 were found per gram of spleen tissue. The data about this guinea pig are not included in the graph. Two guinea pigs, which had no recurrences, were destroyed 20 and 30 days, respectively, after treatment was discontinued, and no tularemia bacteria were found in their organs. In all of the experiments, regardless of the antibiotic used, by the tenth post-infection day the agglutination reaction with tularemic diagnosticum from the ...Shu... strain was positive in serum dilutions from 1:10 to 1:40. Twelve days after infection the titers already constituted 1:160 to 1:320, and by the 20th to 30th days from the start of the experiment they attained 1:320 to 1:1280 and they maintained this level for the entire observation period which ranged from 1½ -- 2 months.

Conclusions

1. Treatment of guinea pigs with Kanamycin, chlortetracycline and streptomycin, at the doses used, begun at the height of the disease caused by infection with 100 lethal doses of a virulent strain of tularemia bacteria was associated from the earliest days of administration with a marked decrease in number of bacteria in the organs and tissues of the animals.

2. Generally, during the first few days after the course of treatment was discontinued, no tularemia bacteria were found in the animals' organs, but in some instances they suffered a recurrence of the disease which was associated with some increase in number of bacteria in the organs.

3. The best results were obtained in the experiments with Kanamycin and streptomycin. The poor therapeutic effect of chlortetracycline was attributed to the insufficient dosage used in view of its toxicity for guinea pigs.

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2. N. G. Olsuf'yev, T. N. Dunayeva, Zh. gig., epidemiol. (Journal of Hygiene, Epidemiology) (Prague), No 3, 1961, page 253.